

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 275 648 A1

(12)

EUROPÄISCHE PATENTANMELDUNG

(43) Veröffentlichungstag:
15.01.2003 Patentblatt 2003/03

(51) Int Cl.7: **C07D 493/04**, C07D 417/06,
C07D 413/06, C07D 277/24
// (C07D493/04, 313:00,
303:00)

(21) Anmeldenummer: 02022332.7

(22) Anmeldetag: 18.06.1999

(84) Benannte Vertragsstaaten:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
Benannte Erstreckungsstaaten:
AL LT LV MK RO SI

(30) Priorität: 18.06.1998 DE 19826988

(62) Dokumentnummer(n) der früheren Anmeldung(en)
nach Art. 76 EPÜ:
99932700.0 / 1 087 975

(71) Anmelder: Gesellschaft für Biotechnologische
Forschung mbH (GBF)
38124 Braunschweig (DE)

(72) Erfinder:
• Höfle, Gerhard, Prof. Dr.
38124 Braunschweig (DE)

- Reichenbach, Hans, Prof. Dr.
38124 Braunschweig (DE)
- Gerth, Klaus, Dr.
38124 Braunschweig (DE)
- Hardt, Ingo, Dr.
38124 Braunschweig (DE)
- Sasse, Florenz, Dr.
38124 Braunschweig (DE)
- Steinmetz, Heinrich
38124 Braunschweig (DE)

(74) Vertreter: Boeters, Hans Dietrich, Dr. et al
Patentanwälte Boeters & Bauer,
Bereiteranger 15
81541 München (DE)

Bemerkungen:

Diese Anmeldung ist am 08 - 10 - 2002 als
Teilanmeldung zu der unter INID-Kode 62
erwähnten Anmeldung eingereicht worden.

(54) **Epothilon-Nebenkomponenten**

(57) Die Erfindung betrifft Verbindungen, die durch Fermentation von DSM 6773 erhältlich sind, insbesondere Epothilone A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3 I4, I5, I6 und K und Trans-Epothilone C1 und C2.

EP 1 275 648 A1

Beschreibung

5 [0001] Die Erfindung betrifft Verbindungen, die im vorliegenden Zusammenhang als Epothilon-Nebenkomponenten bezeichnet werden, und zwar Verbindungen 5 bis 13 und 16 bis 39. Diese Verbindungen lassen sich durch Fermentation von DSM 6773 gemäß DE 41 38 042.8 gewinnen.

[0002] Kenndaten der erfindungsgemäßen Verbindungen sind im folgenden zusammengestellt.

Gewinnung: Die Aufarbeitung eines Rohemothilon-Gemischs, das durch Fermentation von DSM 6773 in einem 900 Liter-Fermentator gewonnen wurde, ist schematisch Fig. 1 bis 2 zu entnehmen.

Aktivitäten: vgl. Tab. 1

10

15

20

25

30

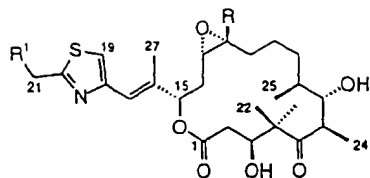
35

40

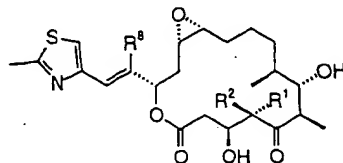
45

50

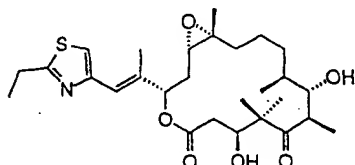
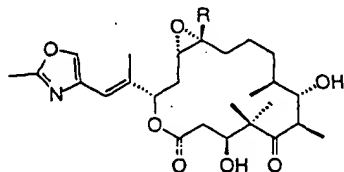
55



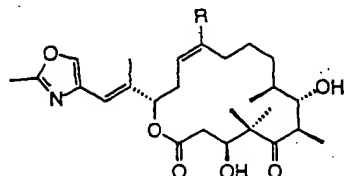
- Epothilone A (1) $R^1 = H$; $R = H$
 Epothilone B (2) $R^1 = H$; $R = Me$
 Epothilone E (3) $R^1 = OH$; $R = H$
 Epothilone F (4) $R^1 = OH$; $R = Me$



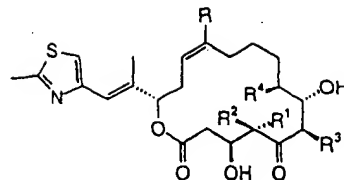
- Epothilone A₁ (5) $R^1 = H$; $R^2, R^8 = Me$
 Epothilone A₂ (6) $R^2 = H$; $R^1, R^8 = Me$
 Epothilone A₈ (7) $R^8 = H$; $R^1, R^2 = Me$
 Epothilone A₉ (8) $R^1 = CH_2OH$; $R^2, R^8 = Me$

Epothilone B₁₀ (9)

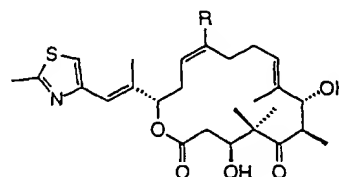
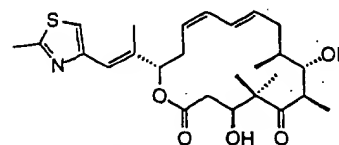
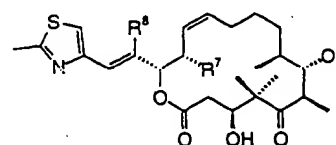
- Epothilone G₁ (10) $R = H$
 Epothilone G₂ (11) $R = Me$



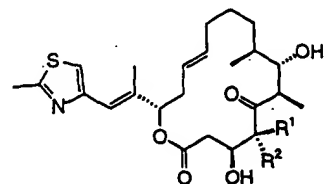
- Epothilone H₁ (12) $R = H$
 Epothilone H₂ (13) $R = Me$



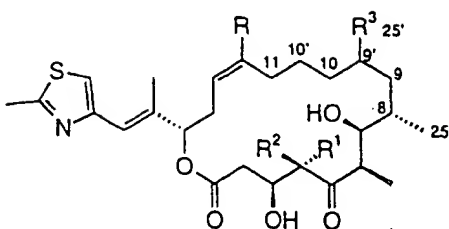
- Epothilone C (14) $R^1, R^2, R^3, R^4 = Me$; $R = H$
 Epothilone D (15) $R^1, R^2, R^3, R^4, R = Me$
 Epothilone C₁ (16) $R^1 = H$; $R^2, R^3, R^4 = Me$; $R = H$
 Epothilone D₁ (17) $R^1 = H$; $R^2, R^3, R^4 = Me$; $R = Me$
 Epothilone C₂ (18) $R^2 = H$; $R^1, R^3, R^4 = Me$; $R = H$
 Epothilone D₂ (19) $R^2 = H$; $R^1, R^3, R^4 = Me$; $R = Me$
 Epothilone C₃ (20) $R^3 = H$; $R^1, R^2, R^4 = Me$; $R = H$
 Epothilone C₄ (21) $R^4 = H$; $R^1, R^2, R^3 = Me$; $R = H$

Epothilone C₃ (22) $R = H$ Epothilone D₃ (23) $R = Me$ Epothilone C₈ (24)

- Epothilone C₇ (25) $R^7 = OH$; $R^8 = Me$
 Epothilone C₈ (26) $R^8, R^7 = H$
 Epothilone C₉ (27) $R^8 = CH_2OH$; $R^7 = H$



- trans-Epothilone C₁ (28) $R^1 = H$; $R^2 = Me$
 trans-Epothilone C₂ (29) $R^2 = H$; $R^1 = Me$



Epothilone I₁ (30) R, R³ = H; R¹, R² = Me

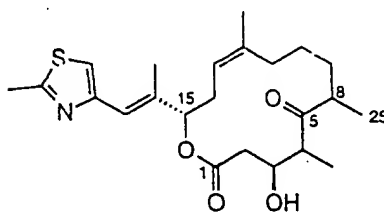
Epothilone I₂ (31) R = H; R¹, R², R³ = Me

Epothilone I₃ (32) R¹, R², R³, R = Me

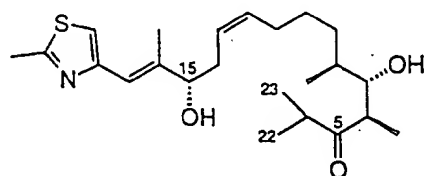
Epothilone I₄ (33) R², R = H; R¹, R³ = Me

Epothilone I₅ (34) R² = H; R¹, R³, R = Me

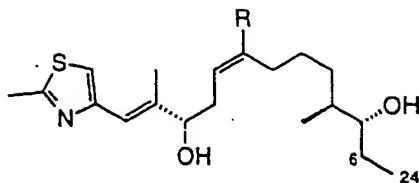
Epothilone I₆ (35) R¹ = H; R², R³, R = Me



Epothilone K (36)



(37)



(38) R = H

(39) R = Me

- [0003] **Epothilone A₁ (5)**: colorless amorphous solid; $[\alpha]_D^{22} -69$ (c 0.1, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 208 (19600), 247 (13600); IR (KBr) ν_{\max} 3437, 2959, 2931, 2876, 1732, 1710, 1455, 1259, 978 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.68 (1H, dd, $J = 4.4, 4.0$ Hz, H-15), 4.12 (1H, m, H-3), 3.71 (1H, m, H-7), 3.52 (1H, bs, 7-OH), 3.37 (1H, bd, $J = 7.5$ Hz, 3-OH), 3.21 (1H, dq, $J = 7.7, 7.0$ Hz, H-4), 3.02 (1H, ddd, $J = 9.2, 4.5, 2.8$ Hz, H-13), 2.87 (1H, ddd, $J = 8.3, 4.5, 3.7$ Hz, H-12), 2.78 (1H, dd, $J = 16.8, 4.3$ Hz, H-2a), 2.70 (3H, s, H-21), 2.66 (1H, dq, $J = 3.9, 7.0$ Hz, H-6), 2.65 (1H, dd, $J = 16.8, 5.2$ Hz, H-2b), 2.16 (1H, ddd, $J = 15.4, 4.4, 2.8$ Hz, H-14a), 2.12 (3H, bs, H-27), 1.91 (1H, ddd, $J = 15.4, 9.2, 4.0$ Hz, H-14b), 1.63 (1H, m, H-10a), 1.62 (2H, m, H-11), 1.59 (1H, m, H-9a), 1.52 (1H, m, H-10b), 1.39 (1H, m, H-8), 1.35 (1H, m, H-9b), 1.211 (3H, d, $J = 7.0$ Hz, H-23), 1.207 (3H, d, $J = 7.0$ Hz, H-24), 0.89 (3H, d, $J = 6.9$ Hz, H-25); EIMS m/z 479 $[\text{M}]^+$ (21), 322 (31), 306 (65), 304 (47), 168 (45), 166 (73), 164 (100), 151 (30), 140 (35); HREIMS m/z 479.2317 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_5\text{S}$, 479.2342).
- [0004] **Epothilone A₂ (6)**: colorless amorphous solid; $[\alpha]_D^{22} +12.0$ (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 210 (15100), 248 (15500); IR (KBr) ν_{\max} 3438, 2963, 2929, 2875, 1734, 1706, 1458, 1262, 981 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.98 (1H, s, H-19), 6.63 (1H, bs, H-17), 5.40 (1H, dd, $J = 8.3, 3.4$ Hz, H-15), 4.26 (1H, ddd, $J = 8.5, 4.8, 4.7$ Hz, H-3), 3.85 (1H, dd, $J = 7.9, 2.6$ Hz, H-7), 3.54 (1H, bs, 3-OH), 3.09 (1H, dq, $J = 4.8, 7.0$ Hz, H-4), 3.01 (1H, ddd, $J = 8.3, 4.8, 4.6$ Hz, H-13), 2.98 (1H, dq, $J = 7.9, 7.0$ Hz, H-6), 2.89 (1H, ddd, $J = 6.7, 4.6, 4.4$ Hz, H-12), 2.68 (3H, s, H-21), 2.60 (1H, dd, $J = 15.1, 8.5$ Hz, H-2a), 2.52 (1H, bs, 7-OH), 2.50 (1H, dd, $J = 15.1, 4.7$ Hz, H-2b), 2.18 (1H, ddd, $J = 15.0, 4.8, 3.4$ Hz, H-14a), 2.11 (3H, d, $J = 1.3$ Hz, H-27), 1.82 (1H, ddd, $J = 15.0, 8.3, 8.1$ Hz, H-14b), 1.63 (1H, m, H-8), 1.61 (2H, m, H-11a and H-10a), 1.46 (1H, m, H-11b), 1.39 (2H, m, H-9), 1.31 (1H, m, H-10b), 1.22 (3H, d, $J = 7.0$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-22), 1.01 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 216.2 (s, C-5), 170.1 (s, C-1), 164.9 (s, C-20), 152.0 (s, C-18), 137.0 (s, C-16), 120.3 (d, C-17), 116.5 (d, C-19), 76.7 (d, C-15), 75.6 (d, C-7), 69.1 (d, C-3), 57.1 (d, C-12), 54.3 (d, C-13), 50.3 (d, C-4), 49.6 (d, C-6), 39.4 (t, C-2), 35.5 (d, C-8), 32.2 (t, C-14), 29.6 (t, C-9), 27.6 (t, C-11), 23.9 (t, C-10), 19.2 (q, C-21), 18.0 (q, C-25), 15.6 (q, C-27), 13.9 (q, C-24), 12.4 (q, C-22); EIMS m/z 479 $[\text{M}]^+$ (18), 322 (38), 306 (78), 304 (59), 168 (48), 166 (96), 164 (100), 151 (33), 140 (38); HREIMS m/z 479.2318 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_5\text{S}$, 479.2342).
- [0005] **Epothilone A₈ (7)**: colorless amorphous solid; $[\alpha]_D^{22} -76.2$ (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 210 (15300), 248 (15500); IR (KBr) ν_{\max} 3440, 2967, 2932, 2876, 1736, 1691, 1467, 1252, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.64 (1H, dd, $J = 15.6, 0.9$ Hz, H-17), 6.52 (1H, dd, $J = 15.6, 6.6$ Hz, H-16), 5.68 (1H, dddd, $J = 7.8, 6.6, 3.2, 0.9$ Hz, H-15), 4.11 (1H, ddd, $J = 10.1, 6.6, 3.5$ Hz, H-3), 3.78 (1H, ddd, $J = 5.2, 3.2, 3.2$ Hz, H-7), 3.66 (1H, d, $J = 6.6$ Hz, 3-OH), 3.23 (1H, dq, $J = 5.2, 6.9$ Hz, H-6), 3.08 (1H, ddd, $J = 7.3, 5.5, 4.1$ Hz, H-13), 2.90 (1H, ddd, $J = 6.6, 4.6, 4.1$ Hz, H-12), 2.69 (3H, s, H-21), 2.52 (1H, dd, $J = 14.7, 10.1$ Hz, H-2a), 2.44 (1H, bd, $J = 3.2$ Hz, 7-OH), 2.41 (1H, dd, $J = 14.7, 3.5$ Hz, H-2b), 2.10 (1H, ddd, $J = 15.0, 5.5, 3.2$ Hz, H-14a), 1.90 (1H, ddd, $J = 15.0, 7.8, 7.3$ Hz, H-14b), 1.71 (1H, m, H-8), 1.65 (1H, m, H-11a), 1.50 (1H, m, H-10a), 1.47 (1H, m, H-11b), 1.40 (2H, m, H-9), 1.39 (1H, m, H-10b), 1.33 (3H, s, H-23), 1.16 (3H, d, $J = 6.9$ Hz, H-24), 1.08 (3H, s, H-22), 0.98 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 75 MHz) δ 220.3 (s, C-5), 170.7 (s, C-1), 166.5 (s, C-20), 152.2 (s, C-18), 128.4 (d, C-16), 125.9 (d, C-17), 116.4 (d, C-19), 75.0 (d, C-7), 73.6 (d, C-3), 72.7 (d, C-15), 57.3 (d, C-12), 54.1 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.9 (t, C-2), 36.3 (d, C-8), 32.5 (t, C-14), 30.3 (t, C-9), 26.7 (t, C-11), 24.0 (t, C-10), 21.3 (q, C-23), 21.0 (q, C-22), 19.3 (q, C-21), 17.1 (q, C-25), 14.5 (q, C-24); EIMS m/z 479 $[\text{M}]^+$ XXX; HRDCIMS m/z 480.2401 (calcd. for $\text{C}_{25}\text{H}_{38}\text{NO}_6\text{S}$, 480.2401).
- [0006] **Epothilone A₉ (8)**: colorless amorphous solid; $[\alpha]_D^{22} -37.6$ (c 0.5, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 211

- (15500), 253 (14100); IR (KBr) ν_{\max} 3423, 2965, 2932, 2877, 1736, 1690, 1463, 1249, 1014, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.10 (1H, s, H-19), 6.72 (1H, dd, $J = 10.7, 4.3$ Hz, 27-OH), 6.60 (1H, bs, H-17), 5.69 (1H, dd, $J = 11.6, 2.0$ Hz, H-15), 5.59 (1H, d, $J = 6.6$ Hz, 3-OH), 4.49 (1H, ddd, $J = 12.9, 4.3, 1.2$ Hz, H-27a), 4.27 (1H, ddd, $J = 11.6, 6.6, 2.9$ Hz, H-3), 4.11 (1H, ddd, $J = 12.9, 10.7, 1.0$ Hz, H-27b), 3.71 (1H, ddd, $J = 4.8, 3.0, 2.8$ Hz, H-7), 3.17 (1H, dq, $J = 3.0, 6.8$ Hz, H-6), 3.04 (1H, ddd, $J = 9.7, 3.6, 2.2$ Hz, H-13), 2.93 (1H, bs, 7-OH), 2.91 (1H, ddd, $J = 9.7, 3.6, 2.7$ Hz, H-12), 2.72 (3H, s, H-21), 2.48 (1H, dd, $J = 14.2, 11.6$ Hz, H-2a), 2.11 (1H, dd, $J = 14.2, 2.9$ Hz, H-2b), 2.03 (1H, ddd, $J = 14.7, 2.2, 2.0$ Hz, H-14a), 1.86 (1H, m, H-11a), 1.85 (1H, m, H-14b), 1.79 (1H, m, H-8), 1.52 (1H, m, H-10a), 1.37 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.36 (1H, in, H-11b), 1.19 (3H, d, $J = 6.8$ Hz, H-24), 1.02 (3H, d, $J = 7.1$ Hz, H-25), 1.00 (3H, s, H-22); ^{13}C NMR (CDCl_3 , 75 MHz) δ 220.5 (s, C-5), 170.2 (s, C-1), 167.5 (s, C-20), 150.7 (s, C-18), 138.9 (s, C-16), 125.2 (d, C-17), 119.5 (d, C-19), 76.7 (d, C-15), 73.4 (d, C-7), 70.4 (d, C-3), 57.7 (d, C-12), 57.2 (t, C-27), 55.3 (d, C-13), 54.2 (s, C-4), 41.3 (d, C-6), 40.7 (t, C-2), 37.5 (d, C-8), 31.8 (t, C-14), 31.2 (t, C-9), 28.0 (t, C-11), 23.7 (q, C-23), 23.2 (t, C-10), 19.2 (q, C-21), 16.8 (q, C-22), 15.8 (q, C-25), 13.5 (q, C-24); EIMS m/z 509 $[\text{M}]^+$ (9), 491 (4), 322 (28), 321 (25), 180 (45), 167 (40), 166 (100), 165 (49), 154 (47), 138 (33); HREIMS m/z 509.2467 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_7\text{S}$, 509.2447).
- [0007] Epothilone B₁₀ (9):** colorless amorphous solid; $[\alpha]_D^{25} -27$ (c 0.15, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 212 (15800), 247 (12500); IR (KBr) ν_{\max} 3434, 2962, 2930, 2876, 2858, 1733, 1692, 1461, 1259, 1052, 981 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 6.99 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.42 (1H, dd, $J = 8.0, 3.0$ Hz, H-15), 4.25 (1H, ddd, $J = 9.5, 6.3, 2.8$ Hz, H-3), 4.23 (1H, bs, 3-OH), 3.77 (1H, ddd, $J = 4.0, 3.9, 3.8$ Hz, H-7), 3.30 (1H, dq, $J = 4.0, 6.9$ Hz, H-6), 3.01 (2H, q, $J = 7.6$ Hz, H-21), 2.81 (1H, dd, $J = 7.7, 4.6$ Hz, H-13), 2.68 (1H, bs, 7-OH), 2.54 (1H, dd, $J = 13.9, 9.5$ Hz, H-2a), 2.36 (1H, dd, $J = 13.9, 2.8$ Hz, H-2b), 2.11 (1H, ddd, $J = 15.3, 4.6, 3.0$ Hz, H-14a), 2.09 (3H, s, H-27), 1.91 (1H, ddd, $J = 15.3, 8.0, 7.7$ Hz, H-14b), 1.74 (1H, m, H-8), 1.73 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.41 (1H, m, H-11b), 1.39 (3H, t, $J = 7.6$ Hz, H-28), 1.38 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.28 (3H, s, H-26), 1.17 (3H, d, $J = 6.9$ Hz, H-24), 1.09 (3H, s, H-22), 1.01 (3H, d, $J = 7.0$ Hz, H-25); EIMS m/z 521 $[\text{M}]^+$ (22), 449 (7), 350 (18), 334 (57), 248 (16), 234 (27), 196 (41), 182 (59), 180 (96), 178 (100), 166 (44), 154 (44); HREIMS m/z 521.2808 (calcd. for $\text{C}_{26}\text{H}_{43}\text{NO}_6\text{S}$, 521.2811).
- [0008] Epothilone G₁ (10):** colorless amorphous solid; $[\alpha]_D^{25} -39.7$ (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 203 (15200), 236 (15100); IR (KBr) ν_{\max} 3456, 2962, 2933, 2876, 1736, 1691, 1585, 1466, 1262, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.47 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.42 (1H, dd, $J = 8.3, 2.9$ Hz, H-15), 4.11 (1H, ddd, $J = 10.1, 6.1, 3.4$ Hz, H-3), 3.78 (1H, bddd, $J = 5.2, 3.5, 3.5$ Hz, H-7), 3.63 (1H, bd, $J = 6.1$ Hz, 3-OH), 3.21 (1H, dq, $J = 5.2, 7.0$ Hz, H-6), 3.00 (1H, ddd, $J = 7.7, 4.8, 4.2$ Hz, H-13), 2.88 (1H, ddd, $J = 7.1, 4.2, 4.2$ Hz, H-12), 2.53 (1H, dd, $J = 14.8, 10.1$ Hz, H-2a), 2.51 (1H, bd, $J = 3.5$ Hz, 7-OH), 2.43 (1H, dd, $J = 14.8, 3.4$ Hz, H-2b), 2.43 (3H, s, H-21), 2.07 (1H, ddd, $J = 15.1, 4.8, 2.9$ Hz, H-14a), 1.99 (3H, d, $J = 1.3$ Hz, H-27), 1.86 (1H, ddd, $J = 15.1, 8.3, 7.7$ Hz, H-14b), 1.71 (1H, m, H-8), 1.69 (1H, m, H-11a), 1.53 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.40 (3H, m, H-9 and H-10b), 1.34 (3H, s, H-23), 1.16 (3H, d, $J = 7.0$ Hz, H-24), 1.09 (3H, s, H-22), 0.99 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.1 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.7 (s, C-16), 135.9 (d, C-19), 116.4 (d, C-17), 76.4 (d, C-15), 74.9 (d, C-7), 73.7 (d, C-3), 57.4 (d, C-12), 54.4 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.8 (t, C-2), 36.2 (d, C-8), 31.4 (t, C-14), 30.4 (t, C-9), 27.0 (t, C-11), 23.9 (t, C-10), 21.3 (q, C-23), 21.2 (q, C-22), 17.2 (q, C-25), 15.8 (q, C-27), 14.4 (q, C-24), 13.8 (q, C-21); EIMS m/z 477 $[\text{M}]^+$ (4), 405 (7), 290 (40), 152 (39), 150 (100), 148 (23), 124 (23); HREIMS m/z 477.2684 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_7$, 477.2727).
- [0009] Epothilone G₂ (11):** colorless amorphous solid; $[\alpha]_D^{25} -22.6$ (c 1.0, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 202 (21500), 236 (14800); IR (KBr) ν_{\max} 3456, 2965, 2934, 2877, 1737, 1690, 1586, 1464, 1250, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.43 (1H, dd, $J = 7.1, 3.6$ Hz, H-15), 4.12 (1H, ddd, $J = 9.9, 6.4, 3.4$ Hz, H-3), 3.77 (1H, ddd, $J = 4.7, 4.4, 4.1$ Hz, H-7), 3.83 (1H, bd, $J = 6.4$ Hz, 3-OH), 3.30 (1H, dq, $J = 4.7, 6.9$ Hz, H-6), 2.78 (1H, dd, $J = 7.0, 5.4$ Hz, H-13), 2.54 (1H, dd, $J = 14.3, 9.9$ Hz, H-2a), 2.51 (1H, bd, $J = 4.1$ Hz, 7-OH), 2.44 (3H, s, H-21), 2.40 (1H, dd, $J = 14.3, 3.4$ Hz, H-2b), 2.03 (1H, ddd, $J = 15.2, 5.4, 3.6$ Hz, H-14a), 2.00 (3H, d, $J = 1.3$ Hz, H-27), 1.92 (1H, ddd, $J = 15.1, 7.1, 7.0$ Hz, H-14b), 1.71 (1H, m, H-8), 1.68 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.39 (3H, m, H-9 and H-10b), 1.35 (3H, s, H-23), 1.26 (3H, s, H-26), 1.16 (3H, d, $J = 6.9$ Hz, H-24), 1.07 (3H, s, H-22), 0.99 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.7 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.5 (s, C-16), 135.9 (d, C-19), 116.3 (d, C-17), 76.6 (d, C-15), 74.6 (d, C-7), 73.5 (d, C-3), 61.3 (s, C-12), 61.1 (d, C-13), 52.7 (s, C-4), 43.4 (d, C-6), 39.0 (t, C-2), 36.5 (d, C-8), 32.0 (t, C-11), 31.8 (t, C-14), 30.8 (t, C-9), 22.8 (t, C-10), 22.9 (q, C-26), 21.0 (q, C-23), 20.8 (q, C-22), 17.2 (q, C-25), 15.9 (q, C-27), 14.1 (q, C-24), 13.8 (q, C-21); EIMS m/z 491 $[\text{M}]^+$ (21), 419 (6), 320 (18), 304 (39), 166 (42), 152 (57), 150 (100), 149 (44), 148 (58), 124 (35), 109 (33); HREIMS m/z 491.2878 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_7$, 491.2883).
- [0010] Epothilone H₁ (12):** colorless amorphous solid; $[\alpha]_D^{25} -84.2$ (c 0.2, MeOH); UV (MeOH) λ_{\max} nm (ϵ) 203 (19600), 237 (12000); IR (KBr) ν_{\max} 3436, 2933, 2880, 2860, 1734, 1688, 1585, 1251, 1007 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.47 (1H, s, H-19), 6.31 (1H, bs, H-17), 5.43 (1H, ddd, $J = 10.6, 10.2, 4.5$ Hz, H-12), 5.36 (1H, dddd, $J = 10.6, 9.6, 5.0, 1.3$ Hz, H-13), 5.30 (1H, dd, $J = 9.9, 2.0$ Hz, H-15), 4.16 (1H, ddd, $J = 11.2, 5.3, 2.8$ Hz, H-3), 3.73 (1H, ddd, $J = 3.9, 2.5, 2.3$ Hz, H-7), 3.12 (1H, dq, $J = 2.3, 6.9$ Hz, H-6), 2.92 (1H, d, $J = 2.5$ Hz, 7-OH), 2.91 (1H, d, $J = 5.3$

- Hz, 7-OH), 2.66 (1H, ddd, $J = 15.1, 9.9, 9.6$ Hz, H-14a), 2.50 (1H, dd, $J = 15.4, 11.2$ Hz, H-2a), 2.43 (3H, s, H-21), 2.37 (1H, dd, $J = 15.4, 2.8$ Hz, H-2b), 2.23 (1H, m, H-14b), 2.18 (1H, m, H-11a), 2.01 (1H, m, H-11b), 2.08 (3H, d, $J = 1.3$ Hz, H-27), 1.74 (1H, m, H-8), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-9a), 1.31 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.17 (3H, d, $J = 6.9$ Hz, H-24), 1.08 (3H, s, H-22), 0.99 (3H, d, $J = 7.1$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 461 $[\text{M}]^+$ (6), 310 (5), 274 (10), 273 (7), 171 (63), 152 (100), 148 (18), 111 (15); HREIMS m/z 461.2743 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_6$, 461.2777).
- [0011] Epothilone H₂ (13):** colorless amorphous solid; $[\alpha]_D^{25} -44.4$ (c 0.25, MeOH); UV (MeOH) λ_{max} nm (ϵ) 203 (14500), 236 (12200); IR (KBr) ν_{max} 3436, 2967, 2935, 2880, 1734, 1690, 1586, 1251, 1007 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.46 (1H, s, H-19), 6.30 (1H, bs, H-17), 5.23 (1H, dd, $J = 9.8, 2.1$ Hz, H-15), 5.12 (1H, dd, $J = 10.1, 5.3$ Hz, H-13), 4.20 (1H, ddd, $J = 10.8, 5.7, 2.9$ Hz, H-3), 3.71 (1H, ddd, $J = 3.8, 2.6, 2.6$ Hz, H-7), 3.14 (1H, dq, $J = 2.6, 6.9$ Hz, H-6), 2.93 (d, $J = 5.7$ Hz, 3-OH), 2.90 (1H, bd, $J = 2.6$ Hz, 7-OH), 2.62 (1H, ddd, $J = 15.1, 9.8, 9.8$ Hz, H-14a), 2.46 (1H, dd, $J = 15.1, 10.8$ Hz, H-2a), 2.43 (3H, s, H-21), 2.32 (1H, dd, $J = 15.1, 2.9$ Hz, H-2b), 2.29 (1H, m, H-11a), 2.19 (1H, bd, $J = 15.1$ Hz, H-14b), 1.97 (3H, d, $J = 1.3$ Hz, H-27), 1.87 (1H, m, H-11b), 1.73 (1H, m, H-8), 1.67 (1H, m, H-10a), 1.65 (3H, bs, H-26), 1.32 (3H, s, H-23), 1.26 (2H, m, H-9), 1.24 (1H, m, H-10b), 1.18 (3H, d, $J = 6.9$ Hz, H-24), 1.07 (3H, s, H-22), 1.00 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.6 (s, C-5), 170.3 (s, C-1), 161.0 (s, C-20), 138.6 (s, C-12), 138.4 (s, C-16), 137.5 (s, C-18), 135.6 (d, C-19), 120.8 (d, C-13), 115.8 (d, C-17), 78.9 (d, C-15), 74.3 (d, C-7), 72.7 (d, C-3), 53.3 (s, C-4), 42.0 (d, C-6), 39.6 (t, C-2), 38.6 (d, C-8), 32.4 (t, C-14), 31.9 (t, C-9), 31.6 (t, C-11), 25.6 (t, C-10), 23.0 (q, C-26), 22.8 (q, C-23), 18.8 (q, C-22), 16.1 (q, C-27), 15.9 (q, C-25), 13.8 (q, 0.21), 13.6 (q, C-24); EIMS m/z 475 $[\text{M}]^+$ (11), 288 (9), 287 (5), 188 (7), 171 (32), 152 (100), 111 (10); HREIMS m/z 475.2913 (calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_6$, 475.2934).
- [0012] Epothilone C₁ (16):** colorless amorphous solid; $[\alpha]_D^{25} -114.0$ (c 10.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 211 (16500), 248 (12500); IR (KBr) ν_{max} 3440, 2933, 2877, 2858, 1730, 1708, 1457, 1244, 981 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.47 (1H, dd, $J = 9.2, 3.0$ Hz, H-15), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 4.40 (1H, ddd, $J = 6.2, 6.1, 6.1$ Hz, H-3), 3.69 (1H, dd, $J = 5.7, 3.6$ Hz, H-7), 3.01 (1H, dq, $J = 5.7, 6.9$ Hz, H-6), 3.01 (1H, bs, 3-OH), 2.84 (1H, dq, $J = 5.2, 7.0$ Hz, H-4), 2.68 (3H, s, H-21), 2.66 (1H, ddd, $J = 16.4, 9.2, 7.3$ Hz, H-14a), 2.64 (1H, dd, $J = 15.9, 7.1$ Hz, H-2a), 2.54 (1H, dd, $J = 15.9, 6.1$ Hz, H-2b), 2.38 (1H, bd, $J = 16.4$ Hz, H-14b), 2.35 (1H, bs, 7-OH), 2.07 (3H, bs, H-27), 2.03 (2H, m, H-11), 1.62 (1H, m, H-10a), 1.53 (1H, m, H-8), 1.35 (1H, m, H-9a), 1.22 (1H, m, H-9b), 1.19 (3H, d, $J = 6.9$ Hz, H-24), 1.14 (3H, d, $J = 6.9$ Hz, H-23), 1.10 (1H, m, H-10b), 0.95 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (5), 324 (8), 290 (8), 204 (7), 168 (100), 164 (15), 139 (36); HREIMS m/z 463.2381 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- [0013] Epothilone D₁ (17):** colorless amorphous solid; $[\alpha]_D^{25} -118.6$ (c 0.5, MeOH); UV (MeOH) λ_{max} nm (ϵ) 208 (18300), 249 (11900); IR (KBr) ν_{max} 3439, 2965, 2934, 2877, 1729, 1707, 1456, 1250, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.98 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.51 (1H, dd, $J = 9.5, 3.4$ Hz, H-15), 5.16 (1H, dd, $J = 8.0, 4.2$ Hz, H-13), 4.42 (1H, ddd, $J = 7.1, 6.3, 5.5$ Hz, H-3), 3.70 (1H, dd, $J = 6.5, 2.9$ Hz, H-7), 3.07 (1H, dq, $J = 6.5, 6.9$ Hz, H-6), 2.95 (1H, dq, $J = 4.7, 7.0$ Hz, H-4), 2.71 (3H, s, H-21), 2.69 (1H, dd, $J = 16.0, 6.3$ Hz, H-2a), 2.64 (1H, m, H-14a), 2.59 (1H, dd, $J = 16.0, 7.1$ Hz, H-2b), 2.46 (1H, bs, 3-OH), 2.38 (1H, bd, $J = 16.0$ Hz, H-14b), 2.19 (1H, ddd, $J = 13.3, 8.6, 5.7$ Hz, H-11a), 2.10 (3H, d, $J = 1.4$ Hz, H-27), 2.02 (1H, bs, 7-OH), 1.91 (1H, ddd, $J = 13.3, 6.0, 6.0$ Hz, H-11b), 1.68 (1H, m, H-10a), 1.66 (3H, bs, H-26), 1.53 (1H, m, H-8), 1.37 (1H, m, H-9a), 1.26 (1H, m, H-9b), 1.24 (3H, d, $J = 6.9$ Hz, H-24), 1.19 (1H, m, H-10b), 1.14 (3H, d, $J = 7.0, 6.9$ Hz, H-23), 0.99 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 217.0 (s, C-5), 169.7 (s, C-1), 165.0 (s, C-20), 152.2 (s, C-18), 138.5 (s, C-12), 137.7 (s, C-16), 120.7 (d, C-13), 120.1 (d, C-17), 116.3 (d, C-19), 78.8 (d, C-15), 77.2 (d, C-7), 67.7 (d, C-3), 52.1 (d, C-4), 46.5 (d, C-6), 40.6 (t, C-2), 37.6 (d, C-8), 32.3 (t, C-14), 31.8 (t, C-11), 29.5 (t, C-9), 25.5 (t, C-10), 23.1 (q, C-26), 19.2 (q, C-21), 15.5 (q, C-27), 16.6 (q, C-25), 14.5 (q, C-24), 9.7 (q, C-23); EIMS m/z 477 $[\text{M}]^+$ (13), 304 (19), 303 (31), 218 (40), 204 (41), 168 (100), 164 (45), 157 (25), 139 (18); HREIMS m/z 477.2544 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 477.2549).
- [0014] Epothilone C₂ (18):** colorless amorphous solid; $[\alpha]_D^{25} -11.6$ (c 10.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 212 (15500), 249 (12100); IR (KBr) ν_{max} 3428, 2962, 2929, 2877, 2859, 1734, 1705, 1460, 1251, 982 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.99 (1H, s, H-19), 6.66 (1H, bs, H-17), 5.55 (1H, ddd, $J = 10.4, 9.2, 6.1$ Hz, H-12), 5.38 (1H, ddd, $J = 10.4, 9.3, 6.2$ Hz, H-13), 5.22 (1H, dd, $J = 8.8, 2.8$ Hz, H-15), 4.42 (1H, dddd, $J = 9.4, 5.6, 4.2, 4.1$ Hz, H-3), 3.93 (1H, d, $J = 5.6$ Hz, 3-OH), 3.86 (1H, m, H-7), 3.15 (1H, bs, 7-OH), 3.12 (1H, dq, $J = 4.2, 7.0$ Hz, H-4), 3.00 (1H, dq, $J = 6.9, 7.0$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dddd, $J = 15.1, 9.3, 8.8, 0.8$ Hz, H-14a), 2.58 (1H, dd, $J = 15.4, 9.4$ Hz, H-2a), 2.38 (1H, dd, $J = 15.4, 4.1$ Hz, H-2b), 2.31 (1H, ddd, $J = 15.1, 6.2, 2.8$ Hz, H-14b), 2.08 (3H, d, $J = 1.3$ Hz, H-27), 2.15 (1H, m, H-11a), 2.04 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.59 (1H, m, H-10a), 1.43 (1H, m, H-9a), 1.31 (1H, m, H-9b), 1.26 (3H, d, $J = 7.0$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-23), 1.11 (1H, m, H-10b), 1.00 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (7), 324 (7), 306 (8), 290 (17), 168 (100), 164 (14), 139 (27); HREIMS m/z 463.2392 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- [0015] Epothilone D₂ (19):** colorless amorphous solid; $[\alpha]_D^{25} -12.5$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 210 (15400), 248 (11200); IR (KBr) ν_{max} 3436, 2965, 2930, 2877, 1732, 1705, 1458, 1253, 980 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.97 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.18 (1H, dd, $J = 7.9, 4.9$ Hz, H-15), 5.18 (1H, ddd, $J = 9.6, 5.4, 1.0$ Hz,

- H-13), 4.27 (1H, m, H-3), 3.88 (1H, dd, $J = 5.6, 4.6$ Hz, H-7), 3.19 (1H, bs, 3-OH), 3.07 (1H, dq, $J = 4.3, 7.0$ Hz, H-4), 2.95 (1H, dq, $J = 5.6, 7.0$ Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, $J = 14.9, 7.8$ Hz, H-2a), 2.56 (1H, ddd, $J = 14.7, 9.6, 7.9$ Hz, H-14a), 2.43 (1H, dd, $J = 14.9, 5.6$ Hz, H-2b), 2.38 (1H, bs, 7-OH), 2.26 (1H, ddd, $J = 14.5, 5.4, 4.9$ Hz, H-14b), 2.19 (1H, ddd, $J = 13.0, 10.4, 5.4$ Hz, H-11a), 2.10 (3H, d, $J = 1.4$ Hz, H-27), 1.95 (1H, ddd, $J = 13.0, 10.3, 5.3$ Hz, H-11b), 1.72 (1H, m, H-8), 1.68 (3H, bs, H-26), 1.61 (1H, m, H-10a), 1.39 (2H, m, H-9), 1.21 (1H, m, H-10b), 1.19 (3H, d, $J = 6.9$ Hz, H-24), 1.17 (3H, d, $J = 7.0, 7.0$ Hz, H-22), 1.00 (3H, d, $J = 6.9$ Hz, H-25); ^{13}C NMR (CDCl_3 , 100 MHz) δ 216.8 (s, C-5), 170.4 (s, C-1), 164.9 (s, C-20), 152.3 (s, C-18), 139.8 (s, C-12), 137.5 (s, C-16), 120.5 (d, C-17), 119.2 (d, C-13), 116.3 (d, C-19), 80.0 (d, C-15), 74.3 (d, C-7), 69.7 (d, C-3), 48.6 (d, C-4), 48.4 (d, C-6), 39.9 (t, C-2), 36.6 (d, C-8), 32.2 (t, C-14), 32.7 (t, C-11), 30.9 (t, C-9), 26.0 (t, C-10), 23.6 (q, C-26), 19.2 (q, C-21), 15.4 (q, C-27), 17.1 (q, C-25), 12.4 (q, C-24), 12.7 (q, C-23); EIMS m/z 477 $[\text{M}]^+$ (22), 304 (19), 303 (17), 218 (22), 204 (25), 168 (100), 164 (28), 157 (31), 139 (21); HREIMS m/z 477.2545 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 477.2549).
- [0016] Epothilone C₃ (20):** colorless amorphous solid; $[\alpha]_D^{22} -62.1$ (c 5.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 212 (16200), 248 (12300); IR (KBr) ν_{max} 3432, 2928, 2878, 2858, 1736, 1698, 1252, 1040 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.95 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.44 (1H, ddd, $J = 10.9, 10.3, 5.4$ Hz, H-12), 5.33 (1H, ddd, $J = 10.9, 9.3, 4.6$ Hz, H-13), 5.23 (1H, dd, $J = 9.5, 2.2$ Hz, H-15), 4.36 (1H, ddd, $J = 11.3, 5.6, 2.3$ Hz, H-3), 4.04 (1H, d, $J = 5.6$ Hz, 3-OH), 3.93 (1H, ddd, $J = 9.5, 2.3, 1.4$ Hz, H-7), 3.56 (1H, bd, $J = 2.3$ Hz, 7-OH), 2.70 (1H, dd, $J = 18.0, 1.4$ Hz, H-6a), 2.67 (3H, s, H-21), 2.61 (1H, ddd, $J = 15.3, 9.5, 9.3$ Hz, H-14a), 2.38 (1H, dd, $J = 14.3, 11.3$ Hz, H-2a), 2.36 (1H, dd, $J = 18.0, 9.5$ Hz, H-6b), 2.28 (1H, bd, $J = 15.3$ Hz, H-14b), 2.12 (1H, m, H-11a), 2.06 (1H, dd, $J = 14.3, 2.3$ Hz, H-2b), 2.03 (3H, d, $J = 1.3$ Hz, H-27), 1.96 (1H, m, H-11b), 1.75 (1H, m, H-8), 1.54 (1H, m, H-10a), 1.26 (1H, m, H-9a), 1.25 (3H, s, H-23), 1.17 (1H, m, H-10b), 1.15 (1H, m, H-9b), 1.03 (3H, s, H-22), 0.91 (3H, d, $J = 6.8$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (28), 290 (14), 168 (100), 164 (36), 157 (44), 151 (25); HREIMS m/z 463.2379 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- [0017] Epothilone C₄ (21):** colorless amorphous solid; $[\alpha]_D^{22} -75.6$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 212 (17200), 248 (12500); IR (KBr) ν_{max} 3434, 2974, 2932, 2859, 1735, 1686, 1252, 1046 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 5.26 (1H, dd, $J = 9.6, 2.3$ Hz, H-15), 4.41 (1H, ddd, $J = 11.4, 5.8, 2.5$ Hz, H-3), 3.78 (1H, m, H-7), 3.70 (1H, bs, 3-OH), 3.46 (1H, d, $J = 0.9$ Hz, 7-OH), 3.01 (1H, dq, $J = 0.5, 7.0$ Hz, H-6), 2.69 (3H, s, H-21), 2.66 (1H, ddd, $J = 15.3, 9.6, 8.8$ Hz, H-14a), 2.47 (1H, dd, $J = 14.5, 11.4$ Hz, H-2a), 2.29 (1H, m, H-14b), 2.25 (1H, dd, $J = 14.5, 2.5$ Hz, H-2b), 2.24 (1H, m, H-11a), 2.07 (3H, d, $J = 1.4$ Hz, H-27), 1.96 (1H, m, H-11b), 1.51 (2H, m, H-8), 1.44 (2H, m, H-10), 1.37 (2H, m, H-9), 1.32 (3H, s, H-23), 1.17 (3H, d, $J = 7.0$ Hz, H-24), 1.07 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 463 $[\text{M}]^+$ (7), 276 (15), 171 (33), 168 (100), 164 (23), 151 (22), 111 (13); HREIMS m/z 463.2373 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- [0018] Epothilone C₅ (22):** colorless amorphous solid; $[\alpha]_D^{22} -158.2$ (c 0.5, MeOH); UV (MeOH) λ_{max} nm (ϵ) 205 (19500), 247 (12700); IR (KBr) ν_{max} 3447, 2972, 2927, 1737, 1690, 1450, 1252, 1181, 986 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.93 (1H, s, H-19), 6.48 (1H, bs, H-17), 5.48 (1H, ddd, $J = 10.7, 6.2, 6.2$ Hz, H-12), 5.39 (1H, m, H-13), 5.37 (1H, m, H-9), 5.34 (1H, dd, $J = 8.0, 2.3$ Hz, H-15), 4.29 (1H, dd, $J = 6.0, 2.6$ Hz, H-7), 4.09 (1H, ddd, $J = 10.8, 7.1, 2.9$ Hz, H-3), 3.59 (1H, d, $J = 7.1$ Hz, 3-OH), 3.17 (1H, dq, $J = 6.0, 6.9$ Hz, H-6), 2.68 (3H, s, H-21), 2.54 (1H, ddd, $J = 15.2, 8.1, 8.0$ Hz, H-14a), 2.44 (1H, bs, 7-OH), 2.42 (1H, dd, $J = 15.1, 2.9$ Hz, H-2a), 2.41 (1H, ddd, $J = 15.2, 2.3, 2.3$ Hz, H-14b), 2.34 (1H, dd, $J = 15.1, 10.8$ Hz, H-2b), 2.20 (1H, m, H-10a), 2.18 (2H, m, H-11), 2.12 (1H, m, H-10b), 2.06 (3H, bs, H-27), 1.67 (3H, bs, H-25), 1.27 (3H, s, H-23), 1.21 (3H, d, $J = 6.9$ Hz, H-24), 1.15 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 475 $[\text{M}]^+$ (6), 392 (7), 304 (6), 288 (33), 204 (76), 171 (19), 168 (100), 164 (12); HREIMS m/z 475.2380 (calcd. for $\text{C}_{26}\text{H}_{37}\text{NO}_5\text{S}$, 475.2392).
- [0019] Epothilone D₅ (23):** colorless amorphous solid; $[\alpha]_D^{22} -150$ (c 0.2, MeOH); UV (MeOH) λ_{max} nm (ϵ) 205 (23300), 248 (13600); IR (KBr) ν_{max} 3439, 2967, 2927, 1736, 1690, 1451, 1254, 1181, 987 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.94 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.34 (1H, bs, H-9), 5.29 (1H, dd, $J = 8.0, 2.4$ Hz, H-15), 5.16 (1H, dd, $J = 8.2, 6.2$ Hz, H-13), 4.30 (1H, bd, $J = 4.9$ Hz, H-7), 4.19 (1H, ddd, $J = 10.8, 7.6, 3.0$ Hz, H-3), 3.68 (1H, d, $J = 7.6$ Hz, 3-OH), 3.17 (1H, dq, $J = 4.9, 7.0$ Hz, H-6), 2.69 (3H, s, H-21), 2.65 (1H, d, $J = 2.1$ Hz, 7-OH), 2.56 (1H, ddd, $J = 16.2, 8.2, 8.0$ Hz, H-14a), 2.40 (1H, dd, $J = 15.0, 3.0$ Hz, H-2a), 2.39 (1H, bd, $J = 16.2$ Hz, H-14b), 2.34 (1H, dd, $J = 15.0, 10.8$ Hz, H-2b), 2.25 (2H, m, H-10a and H-11a), 2.20 (1H, m, H-10b), 2.17 (1H, m, H-11b), 2.05 (3H, d, $J = 1.0$ Hz, H-27), 1.69 (3H, bs, H-25), 1.68 (3H, bs, H-26), 1.29 (3H, s, H-23), 1.23 (3H, d, $J = 7.0$ Hz, H-24), 1.16 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 489 $[\text{M}]^+$ (4), 406 (4), 338 (7), 302 (13), 218 (35), 171 (10), 168 (100), 153 (20), 125 (10); HREIMS m/z 489.2536 (calcd. for $\text{C}_{27}\text{H}_{39}\text{NO}_5\text{S}$, 489.2549).
- [0020] Epothilone C₆ (24):** colorless amorphous solid; $[\alpha]_D^{22} -205.2$ (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ϵ) 218 (24600), 237 (28800); IR (KBr) ν_{max} 3435, 2967, 2927, 1732, 1688, 1465, 1258, 988 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.97 (1H, s, H-19), 6.58 (1H, bs, H-17), 6.43 (1H, dd, $J = 15.5, 10.8$ Hz, H-11), 6.11 (1H, dd, $J = 10.8, 10.6$ Hz, H-12), 5.75 (1H, ddd, $J = 15.5, 8.3, 5.6$ Hz, H-10), 5.34 (1H, m, H-13), 5.34 (1H, dd, $J = 9.7, 2.4$ Hz, H-15), 4.16 (1H, ddd, $J = 9.2, 4.9, 4.3$ Hz, H-3), 3.74 (1H, ddd, $J = 2.2, 2.1, 1.7$ Hz, H-7), 3.24 (1H, dq, $J = 2.1, 6.9$ Hz, H-6), 3.06 (1H, d, $J = 2.2$ Hz, 7-OH), 2.93 (1H, d, $J = 4.9$ Hz, 3-OH), 2.78 (1H, dddd, $J = 14.1, 9.9, 9.7, 0.7$ Hz, H-14a), 2.71 (3H, s, H-21), 2.48 (1H, m, H-9a), 2.47 (1H, dd, $J = 15.5, 9.2$ Hz, H-2a), 2.40 (1H, dd, $J = 15.5, 4.3$ Hz, H-2b), 2.38 (1H, bdd, $J = 14.1, 7.8$

- Hz, H-14b), 2.11 (3H, d, $J = 1.3$ Hz, H-27), 1.96 (1H, m, H-8), 1.33 (3H, s, H-23), 1.11 (3H, d, $J = 6.9$ Hz, H-24), 1.06 (3H, s, H-22), 1.05 (3H, d, $J = 6.8$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 475 [M] $^+$ (13), 387 (2), 316 (4), 288 (15), 230 (16), 204 (9), 171 (18), 168 (100), 164 (14), 151 (17); HREIMS m/z 475.2361 (calcd. for $\text{C}_{26}\text{H}_{37}\text{NO}_5\text{S}$, 475.2392).
- 5 [0021] Epothilone **C₇** (25): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c 2.0, MeOH); UV (MeOH) λ_{max} nm (ε) XXX (XXX), XXX (XXX); IR (KBr) ν_{max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.01 (1H, s, H-19), 6.66 (1H, bs, H-17), 5.59 (1H, ddd, $J = 11.1, 11.1, 3.8$ Hz, H-12), 5.40 (1H, dd, $J = 11.1, 9.2$, H-13), 5.03 (1H, d, $J = 9.3$ Hz, H-15), 4.62 (1H, dd, $J = 9.3, 9.2$ Hz, H-14), 4.18 (1H, bd, $J = 11.0$ Hz, H-3), 3.72 (1H, bs, H-7), 3.20 (1H, bs, 3-OH), 3.09 (1H, dq, $J = 1.9, 6.8$ Hz, H-6), 3.00 (1H, bs, 7-OH), 2.69 (3H, s, H-21), 2.47 (1H, dd, $J = 14.8, 11.0$ Hz, H-2a), 2.32 (1H, dd, $J = 14.8, 2.6$ Hz, H-2b), 2.27 (1H, m, H-11a), 2.19 (3H, bs, H-27), 2.13 (1H, m, H-11b), 1.76 (1H, m, H-8), 1.70 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.32 (3H, s, H-23), 1.23 (1H, m, H-9b), 1.21 (1H, m, H-10b), 1.18 (3H, d, $J = 6.8$ Hz, H-24), 1.08 (3H, s, H-22), 1.00 (3H, d, $J = 6.9$ Hz, H-25); EIMS m/z 493 [M] $^+$ XXX; HREIMS m/z 493.XXX (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 493.2498).
- 10 [0022] Epothilone **C₈** (26): colorless amorphous solid; $[\alpha]_D^{22}$ -75.2 (c 2.5, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (16800), 248 (17800); IR (KBr) ν_{max} 3443, 2932, 2881, 1734, 1689, 1465, 1255, 1183, 976 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.93 (1H, s, H-19), 6.62 (1H, dd, $J = 15.6, 0.6$ Hz, H-17), 6.49 (1H, dd, $J = 15.6, 6.6$ Hz, H-16), 5.52 (1H, dddd, $J = 9.5, 6.6, 2.8, 0.6$ Hz, H-15), 5.42 (1H, m, H-12), 5.41 (1H, m, H-13), 4.13 (1H, ddd, $J = 11.0, 5.3, 2.8$ Hz, H-3), 3.69 (1H, ddd, $J = 3.7, 2.8, 2.5$ Hz, H-7), 3.11 (1H, dq, $J = 2.5, 6.8$ Hz, H-6), 2.95 (1H, d, $J = 5.3$ Hz, 3-OH), 2.90 (1H, d, $J = 2.8$ Hz, 7-OH), 2.69 (3H, s, H-21), 2.67 (1H, ddd, $J = 14.9, 9.5, 8.4$ Hz, H-14a), 2.48 (1H, dd, $J = 15.6, 11.0$ Hz, H-2a), 2.33 (1H, dd, $J = 15.6, 2.8$ Hz, H-2b), 2.30 (1H, bd, $J = 14.9$ Hz, H-14b), 2.14 (1H, m, H-11a), 2.03 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.31 (1H, m, H-9a), 1.29 (3H, s, H-23), 1.17 (3H, d, $J = 6.8$ Hz, H-24), 1.16 (1H, m, H-10b), 1.14 (1H, m, H-9b), 1.05 (3H, s, H-22), 0.97 (3H, d, $J = 7.1$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 [M] $^+$ (21), 310 (10), 276 (21), 171 (83), 154 (100), 150 (27), 111 (18); HREIMS m/z 463.2382 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- 15 [0023] Epothilone **C₉** (27): colorless amorphous solid; $[\alpha]_D^{22}$ -93.4 (c 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 209 (15200), 254 (15700); IR (KBr) ν_{max} 3416, 2966, 2932, 1736, 1689, 1463, 1249, 1011 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.06 (1H, s, H-19), 6.65 (1H, bs, H-17), 6.56 (1H, dd, $J = 10.6, 4.4$ Hz, 27-OH), 5.55 (1H, d, $J = 6.2$ Hz, 3-OH), 5.52 (1H, dd, $J = 11.6, 2.0$ Hz, H-15), 5.44 (1H, dddd, $J = 11.2, 10.7, 3.1, 1.7$ Hz, H-12), 5.35 (1H, dddd, $J = 11.0, 10.7, 3.9, 1.7$ Hz, H-13), 4.47 (1H, dd, $J = 12.5, 4.4, 1.3$ Hz, H-27a), 4.35 (1H, ddd, $J = 11.7, 6.2, 2.6$ Hz, H-3), 4.20 (1H, ddd, $J = 12.5, 10.6, 0.9$ Hz, H-27b), 3.63 (1H, ddd, $J = 4.6, 1.8, 0.9$ Hz, H-7), 3.24 (1H, d, $J = 1.8$ Hz, 7-OH), 3.13 (1H, dq, $J = 0.9, 6.8$ Hz, H-6), 2.80 (1H, ddd, $J = 14.8, 11.6, 11.0$ Hz, H-14a), 2.71 (3H, s, H-21), 2.40 (1H, dd, $J = 14.4, 11.7$ Hz, H-2a), 2.24 (1H, m, H-11a), 2.06 (1H, dd, $J = 14.4, 2.6$ Hz, H-2b), 2.01 (1H, ddd, $J = 14.8, 3.9, 2.0$ Hz, H-14b), 2.00 (1H, m, H-11b), 1.77 (1H, m, H-8), 1.69 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.35 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.19 (3H, d, $J = 6.8$ Hz, H-24), 1.18 (1H, m, H-9b), 1.01 (3H, d, $J = 7.1$ Hz, H-25), 0.98 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS m/z 493 [M] $^+$ (17), 306 (64), 184 (50), 171 (30), 167 (38), 166 (100), 138 (12); HREIMS m/z 493.2502 (calcd. for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$, 493.2498).
- 20 [0024] trans-Epothilone **C₁** (28): colorless amorphous solid; $[\alpha]_D^{22}$ -84 (c 0.2, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (17400), 248 (12900); IR (KBr) ν_{max} 3433, 2961, 2933, 2879, 1730, 1708, 1457, 1251, 975 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 7.00 (1H, s, H-19), 6.64 (1H, bs, H-17), 5.45 (1H, ddd, $J = 15.2, 6.5, 6.5$ Hz, H-12), 5.42 (1H, dd, $J = 6.4, 3.7$ Hz, H-15), 5.35 (1H, dt, $J = 15.2, 7.1$ Hz, H-13), 4.42 (1H, m, H-3), 3.58 (1H, ddd, $J = 8.1, 7.9, 2.8$ Hz, H-7), 3.24 (1H, m, H-6), 3.14 (1H, dq, $J = 4.0, 6.9$ Hz, H-6), 2.92 (1H, d, $J = 7.9$ Hz, 7-OH), 2.71 (3H, s, H-21), 2.71 (2H, m, H-2), 2.53 (2H, m, H-14), 2.17 (1H, d, $J = 2.17$ Hz, 3-OH), 2.11 (1H, m, H-11a), 2.06 (3H, bs, H-27), 1.93 (1H, m, H-11b), 1.68 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-8), 1.26 (3H, d, $J = 6.8$ Hz, H-24), 1.16 (1H, m, H-10b), 1.12 (3H, d, $J = 6.9$ Hz, H-22), 1.07 (1H, m, H-9b), 1.00 (3H, d, $J = 6.8$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 [M] $^+$ (6), 290 (21), 289 (20), 204 (23); 194 (19), 190 (22), 168 (100), 164 (48), 157 (14), 152 (19), 151 (17), 139 (15), 111 (18); HREIMS m/z 463.2371 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- 25 [0025] trans-Epothilone **C₂** (29): colorless amorphous solid; $[\alpha]_D^{22}$ -3 (c 1.5, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (15800), 248 (11900); IR (KBr) ν_{max} 3435, 2963, 2931, 2878, 1731, 1706, 1457, 1273, 979 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 6.99 (1H, s, H-19), 6.57 (1H, bs, H-17), 5.56 (1H, ddd, $J = 15.1, 7.4, 7.0$ Hz, H-12), 5.41 (1H, ddd, $J = 15.1, 7.0, 6.9$ Hz, H-13), 5.41 (1H, dd, $J = 7.7, 2.8$ Hz, H-15), 4.13 (1H, dddd, $J = 6.7, 6.2, 5.6, 5.1$ Hz, H-3), 3.78 (1H, ddd, $J = 8.2, 6.5, 1.9$ Hz, H-7), 3.18 (1H, d, $J = 5.6$ Hz, 3-OH), 3.06 (1H, dq, $J = 8.2, 7.1$ Hz, H-6), 2.98 (1H, dq, $J = 6.2, 7.0$ Hz, H-4), 2.71 (3H, s, H-21), 2.64 (1H, dd, $J = 15.1, 6.7$ Hz, H-2a), 2.54 (1H, dd, $J = 15.1, 5.1$ Hz, H-2b), 2.44 (2H, m, H-14), 2.22 (1H, dddd, $J = 13.8, 7.0, 6.2, 2.9$ Hz, H-11a), 2.10 (3H, d, $J = 1.1$ Hz, H-27), 2.09 (1H, d, $J = 6.5$ Hz, 7-OH), 1.88 (1H, dddd, $J = 13.8, 10.9, 7.4, 2.9$ Hz, H-11b), 1.65 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.56 (1H, dddd, $J = 12.7, 12.7, 3.9, 3.9$ Hz, H-9a), 1.20 (3H, d, $J = 7.1$ Hz, H-24), 1.15 (3H, d, $J = 7.0$ Hz, H-23), 1.13 (1H, m, H-10b), 1.04 (1H, m, H-9b), 1.01 (3H, d, $J = 7.0$ Hz, H-25); ^{13}C NMR, see Table 1; EIMS m/z 463 [M] $^+$ (13), 290 (11), 190 (10), 168 (100), 164 (20), 157 (26), 139 (17); HREIMS m/z 463.2383 (calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_5\text{S}$, 463.2392).
- 30 [0026] Epothilone **I₁** (30): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{max} nm (ε) XXX;

- IR (KBr) ν_{\max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.96 (1H, s, H-19), 6.54 (1H, bs, H-17), 5.49 (1H, ddd, J = 10.3, 7.3, 7.3 Hz, H-12), 5.33 (1H, dd, J = 8.3, 4.4 Hz, H-15), 5.31 (1H, m, H-13), 4.15 (1H, ddd, J = 8.0, 5.0, 4.6 Hz, H-3), 3.80 (1H, m, H-7), 3.21 (1H, dq, J = 6.0, 6.9 Hz, H-6), 2.89 (1H, d, J = 5.0 Hz, 3-OH); 2.70 (3H, s, H-21), 2.65 (1H, ddd, J = 15.8, 8.5, 8.3 Hz, H-14a), 2.42 (2H, m, H-2), 2.35 (1H, m, H-14b), 2.27 (1H, bd, J = 3.3 Hz, 7-OH), 2.13 (1H, m, H-11a), 2.09 (3H, d, J = 1.2 Hz, H-27), 2.00 (1H, m, H-11b), 1.72 (1H, m, H-8), 1.40 (2H, m, H-10 β), 1.37 (1H, m, H-9 β a), 1.36 (2H, m, H-9 α), 1.32 (3H, s, H-23), 1.27 (3H, m, H-9 β b and H-10 α), 1.13 (3H, d, J = 6.9 Hz, H-24), 1.09 (3H, s, H-22), 0.94 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR (CDCl_3 , 75 MHz) δ 221.3 (s, C-5), 171.1 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.4 (s, C-16), 133.8 (d, C-12), 124.6 (d, C-13), 120.0 (d, C-17), 116.2 (d, C-19), 78.8 (d, C-15), 74.9 (d, C-7), 74.7 (d, C-3), 51.6 (s, C-4), 43.7 (d, C-6), 38.9 (t, C-2), 34.3 (d, C-8), 31.6 (t, C-14), 29.3 (t, C-9 α), 28.6 (t, C-10 β), 28.2 (t, C-10 α), 26.6 (t, C-11), 24.8 (t, C-9 β), 23.6 (q, C-22), 19.3 (q, C-21), 16.5 (q, C-25), 15.5 (q, C-27), 13.7 (q, C-24); EIMS m/z 505 $[\text{M}]^+$ XXX; HREIMS m/z 505.XXX (calcd. for $\text{C}_{28}\text{H}_{43}\text{NO}_5\text{S}$, 505.XXX).
- [0027] Epothilone I₂ (31): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.40 (1H, m, H-12), 5.38 (1H, dd, J = 9.8, 3.3 Hz, H-15), 5.37 (1H, m, H-13), 4.21 (1H, ddd, J = 8.6, 3.8, 3.6 Hz, H-3), 3.85 (1H, ddd, J = 8.5, 5.8, 2.2 Hz, H-7), 3.18 (1H, dq, J = 8.5, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.65 (1H, ddd, J = 15.2, 9.8, 9.0 Hz, H-14a), 2.51 (1H, d, J = 3.6 Hz, 3-OH), 2.37 (2H, m, H-2), 2.32 (1H, bd, J = 15.2 Hz, H-14b), 2.09 (3H, d, J = 1.3 Hz, H-27), 2.07 (2H, m, H-11), 1.78 (1H, m, H-8), 1.65 (1H, d, J = 5.8 Hz, 7-OH), 1.57 (1H, m, H-10 β a), 1.44 (1H, m, H-10 α a), 1.42 (1H, m, H-9 β), 1.32 (3H, s, H-23), 1.21 (1H, m, H-10 β b), 1.17 (3H, d, J = 7.0 Hz, H-24), 1.13 (2H, m, H-9 α), 1.06 (3H, s, H-22), 0.95 (3H, d, J = 7.0 Hz, H-25 α), 0.91 (3H, d, J = 6.5 Hz, H-25 β), 0.68 (1H, m, H-10 α b); ^{13}C NMR (CDCl_3 , 100 MHz) δ 220.4 (s, C-5), 171.3 (s, C-1), XXX (s, C-20), 152.4 (s, C-18), 137.6 (s, C-16), 134.5 (d, C-12), 125.3 (d, C-13), 119.6 (d, C-17), 116.2 (d, C-19), 78.6 (d, C-15), 77.2 (d, C-7), 75.0 (d, C-3), 51.0 (s, C-4), 44.6 (d, C-6), 38.2 (t, C-2), 36.9 (t, C-9 α), 34.5 (t, C-10 α), 32.6 (d, C-8), 32.0 (t, C-14), 30.0 (d, C-9 β), 27.4 (t, C-11), 26.6 (t, C-10 β), 25.0 (q, C-22), 21.5 (q, C-25 β), 19.3 (q, C-21), 17.9 (q, C-25 α), 17.7 (q, C-23), 15.8 (q, C-24), 15.6 (q, C-27); EIMS m/z 519 $[\text{M}]^+$ XXX; HREIMS m/z 519.XXX (calcd. for $\text{C}_{29}\text{H}_{45}\text{NO}_5\text{S}$, 519.XXX).
- [0028] Epothilone I₃ (32): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, J = 9.1, 3.0 Hz, H-15), 5.08 (1H, dd, J = 8.5, 3.9 Hz, H-13), 4.13 (1H, ddd, J = 9.4, 4.3, 3.2 Hz, H-3), 3.81 (1H, m, H-7), 3.18 (1H, dq, J = 6.8, 7.0 Hz, H-6), 2.83 (1H, d, J = 4.3 Hz, 3-OH), 2.70 (3H, s, H-21), 2.61 (1H, ddd, J = 15.8, 9.1, 8.5 Hz, H-14a), 2.43 (1H, dd, J = 14.0, 3.2 Hz, H-2a), 2.38 (2H, dd, J = 14.0, 9.4 Hz, H-2b), 2.30 (1H, bd, J = 15.8 Hz, H-14b), 2.16 (1H, ddd, J = 14.1, 8.3, 7.4 Hz, H-11a), 2.08 (3H, d, J = 1.0 Hz, H-27), 1.99 (1H, d, J = 4.7 Hz, 7-OH), 1.92 (1H, ddd, J = 14.1, 6.3, 6.3 Hz, H-11b), 1.82 (1H, m, H-8), 1.67 (3H, s, H-26), 1.51 (1H, m, H-10 β a), 1.40 (1H, m, H-9 β), 1.33 (1H, m, H-10 β b), 1.31 (3H, s, H-23), 1.27 (1H, m, H-10 α a), 1.23 (1H, m, H-9 α a), 1.16 (3H, d, J = 7.0 Hz, H-24), 1.10 (1H, m, H-9 α b), 1.07 (3H, s, H-22), 0.95 (3H, d, J = 7.0 Hz, H-25 α), 0.92 (3H, d, J = 6.5 Hz, H-25 β), 0.75 (1H, m, H-10 α b); EIMS m/z 533 $[\text{M}]^+$ XXX; HREIMS m/z 533.XXX (calcd. for $\text{C}_{30}\text{H}_{47}\text{NO}_5\text{S}$, 533.XXX).
- [0029] Epothilone I₄ (33): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.47 (1H, dt, J = 11.1, 5.8 Hz, H-12), 5.33 (1H, ddd, J = 9.2, 3.9, 0.5 Hz, H-15), 5.33 (1H, m, H-13), 4.09 (1H, dddd, J = 9.6, 8.1, 4.5, 3.3 Hz, H-3), 3.83 (1H, m, H-7), 3.57 (1H, bs, 3-OH), 2.89 (1H, dq, J = 7.4, 7.1 Hz, H-6), 2.83 (1H, dq, J = 8.1, 7.1 Hz, H-4), 2.70 (3H, s, H-21), 2.64 (1H, m, H-14a), 2.42 (1H, dd, J = 14.2, 3.3 Hz, H-2a), 2.43 (1H, dd, J = 14.2, 9.6 Hz, H-2b), 2.30 (1H, m, H-14b), 2.10 (3H, d, J = 1.3 Hz, H-27), 2.09 (2H, m, H-11), 1.81 (1H, m, H-8), 1.74 (1H, bd, J = 5.6 Hz, 7-OH), 1.53 (1H, m, H-10 β a), 1.49 (1H, m, H-9 β), 1.47 (1H, m, H-10 α a), 1.27 (1H, m, H-10 β b), 1.24 (1H, m, H-9 α a), 1.17 (3H, d, J = 7.1 Hz, H-23), 1.14 (1H, m, H-9 α b), 1.08 (3H, d, J = 7.1 Hz, H-24), 0.97 (3H, d, J = 6.9 Hz, H-25 α), 0.91 (3H, d, J = 6.5 Hz, H-25 β), 0.79 (1H, m, H-10 α b); ^{13}C NMR (CDCl_3 , 100 MHz) δ 217.0 (s, C-5), 170.8 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.1 (s, C-16), 134.6 (d, C-12), 124.7 (d, C-13), 120.2 (d, C-17), 116.4 (d, C-19), 78.7 (d, C-15), 76.4 (d, C-7), 71.3 (d, C-3), 50.7 (d, C-4), 50.1 (d, C-6), 40.7 (t, C-2), 38.5 (t, C-9 α), 35.5 (t, C-10 α), 33.4 (d, C-8), 31.8 (t, C-14), 30.0 (d, C-9 β), 27.2 (t, C-11), 26.7 (t, C-10 β), 21.4 (q, C-25 β), 19.3 (q, C-21), 18.2 (q, C-25 α), 15.4 (q, C-27), 14.4 (q, C-24), 13.1 (q, C-23); EIMS m/z 505 $[\text{M}]^+$ XXX; HREIMS m/z 505.XXX (calcd. for $\text{C}_{28}\text{H}_{43}\text{NO}_5\text{S}$, 505.XXX).
- [0030] Epothilone I₅ (34): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.97 (1H, s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, J = 7.1, 6.2 Hz, H-15), 5.03 (1H, dd, J = 8.4, 5.0 Hz, H-13), 4.05 (1H, dddd, J = 7.5, 7.2, 5.9, 4.6 Hz, H-3), 3.91 (1H, m, H-7), 3.17 (1H, d, J = 5.9 Hz, 3-OH), 2.94 (1H, dq, J = 7.2, 7.1 Hz, H-4), 2.87 (1H, dq, J = 6.5, 6.9 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, J = 14.6, 4.6 Hz, H-2a), 2.60 (1H, m, H-14a), 2.53 (1H, dd, J = 14.6, 7.5 Hz, H-2b), 2.31 (1H, m, H-14b), 2.10 (3H, d, J = 1.1 Hz, H-27), 2.10 (1H, m, H-11a), 2.02 (1H, m, H-11b), 1.97 (1H, bd, J = 5.6 Hz, 7-OH), 1.84 (1H, m, H-8), 1.66 (3H, s, H-26), 1.55 (1H, m, H-9 β), 1.49 (1H, m, H-10 β a), 1.39 (1H, m, H-10 β b), 1.33 (1H, m, H-10 α a), 1.31 (1H, m, H-9 α a), 1.15 (3H, d, J = 7.1 Hz, H-23), 1.12 (1H, m, H-9 α b), 1.11 (3H, d, J = 6.9 Hz, H-24), 0.97 (3H, d, J = 6.9 Hz, H-25 α), 0.94 (1H, m, H-10 α b), 0.93 (3H, d, J = 6.6 Hz, H-25 β); EIMS m/z 519 $[\text{M}]^+$ XXX; HREIMS m/z 519.XXX (calcd. for $\text{C}_{29}\text{H}_{45}\text{NO}_5\text{S}$, 519.XXX).

- [0031] Epothilone I₆ (35): colorless amorphous solid; $[\alpha]_D^{22}$ -XXX (c XXX, MeOH); UV (MeOH) λ_{\max} nm (ε) XXX; IR (KBr) ν_{\max} XXX cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.97 (1H, s, H-19), 6.52 (1H, bs, H-17), 5.24 (1H, dd, J = 6.9, 6.9 Hz, H-15), 5.02 (1H, dd, J = 8.8, 5.2 Hz, H-13), 4.22 (1H, tdd, J = 6.1, 5.6, 4.8 Hz, H-3), 3.76 (1H, ddd, J = 6.1, 5.7, 5.6 Hz, H-7), 3.13 (1H, d, J = 5.6 Hz, 3-OH), 3.05 (1H, dq, J = 4.8, 7.0 Hz, H-4), 2.79 (1H, dq, J = 5.6, 6.9 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, m, H-14a), 2.57 (2H, d, J = 6.1 Hz, H-2a), 2.30 (1H, m, H-14b), 2.08 (3H, d, J = 1.0 Hz, H-27), 2.02 (2H, m, H-11), 1.73 (1H, d, J = 6.1 Hz, 7-OH), 1.69 (1H, m, H-8), 1.66 (3H, s, H-26), XXX (H-9_α, H-9_β, H-10_α, H-10_β), 1.21 (3H, d, J = 7.0 Hz, H-22), 1.16 (3H, d, J = 6.9 Hz, H-24), 0.94 (3H, d, J = 6.9 Hz, H-25_α), 0.91 (3H, d, J = 6.4 Hz, H-25_β); EIMS *m/z* 519 [M]⁺ XXX; HREIMS *m/z* 519.XXX (calcd. for C₂₉H₄₅NO₅S, 519.XXX).
- [0032] Epothilone K (36): colorless amorphous solid; $[\alpha]_D^{22}$ -7 (c 0.08, MeOH); UV (MeOH) λ_{\max} nm (ε) 212 (16700), 248 (12500); IR (KBr) ν_{\max} 3431, 2963, 2927, 2856, 1731, 1712, 1262, 1093, 1021, 802 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.95 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.49 (3H, m, H-15, H-13, and H-12), 4.04 (1H, dddd, J = 7.9, 7.6, 6.9, 3.3 Hz, H-3), 3.36 (1H, dq, J = 6.9, 6.8 Hz, H-6), 2.83 (1H, d, J = 7.6 Hz, 3-OH), 2.75 (1H, ddd, J = 16.1, 6.6, 3.4 Hz, H-14a), 2.74 (1H, dd, J = 15.3, 3.3 Hz, H-2a), 2.71 (3H, s, H-21), 2.58 (2H, m, H-14b and H-8), 2.50 (1H, dd, J = 15.3, 7.9 Hz, H-2b), 2.29 (1H, m, H-11a), 2.10 (1H, m, H-11b), 2.09 (3H, d, J = 0.7 Hz, H-27), 1.78 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.48 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.15 (3H, d, J = 6.8 Hz, H-22), 1.03 (3H, d, J = 6.5 Hz, H-25); EIMS *m/z* 405 [M]⁺ (38), 317 (12), 260 (9), 232 (10), 204 (14), 190 (16), 168 (100), 164 (30), 151 (28); HREIMS *m/z* 405.XXX (calcd. for C₂₆H₃₉NO₅S, 405.XXX).
- [0033] (37): colorless amorphous solid; $[\alpha]_D^{22}$ -27.5 (c 0.4, MeOH); UV (MeOH) λ_{\max} nm (ε) 211 (16100), 247 (12100); IR (KBr) ν_{\max} 3431, 2967, 2929, 2875, 1704, 1462, 1381, 1010 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.56 (1H, dtt, J = 10.8, 7.3, 1.4 Hz, H-12), 5.39 (1H, dtt, J = 10.8, 7.3, 1.4 Hz, H-13), 4.17 (1H, t, J = 6.6 Hz, H-15), 3.50 (1H, ddd, J = 8.7, 2.6, 2.6 Hz, H-7), 3.10 (1H, d, J = 2.6, 7-OH), 2.90 (1H, dq, J = 2.6, 7.2 Hz, H-6), 2.77 (1H, sep, J = 6.9 Hz, H-4), 2.70 (3H, s, H-21), 2.40 (2H, m, H-14), 2.07 (2H, m, H-11), 2.04 (3H, d, J = 1.1 Hz, H-27), 1.78 (1H, bs, 15-OH), 1.74 (1H, m, H-9a), 1.50 (1H, m, H-8), 1.46 (1H, m, H-10a), 1.27 (1H, m, H-10b), 1.11 (1H, m, H-9b), 1.094 (3H, d, J = 6.9 Hz, H-23), 1.089 (3H, d, J = 6.9 Hz, H-22), 1.08 (3H, d, J = 7.2 Hz, H-24), 0.82 (3H, d, J = 6.7 Hz, H-25); ¹³C NMR (CDCl₃, 100 MHz) δ 220.5 (s, C-5), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 133.4 (d, C-12), 125.0 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 74.9 (d, C-7), 44.9 (d, C-6), 40.0 (d, C-4), 35.5 (d, C-8), 33.5 (t, C-14), 32.3 (t, C-9), 27.9 (t, C-11), 26.9 (t, C-10), 19.2 (q, C-21), 18.6 (q, C-23), 18.1 (q, C-22), 15.6 (q, C-25), 14.4 (q, C-27), 9.3 (q, C-24); EIMS *m/z* 407 [M]⁺ (0.1), 204 (0.8), 168 (100), 140 (3.4); HREIMS *m/z* 407.XXX (calcd. for C₂₃H₃₇NO₃S, 407.XXX).
- [0034] (38): colorless amorphous solid; $[\alpha]_D^{22}$ +25.0 (c 0.5, MeOH); UV (MeOH) λ_{\max} nm (ε) 212 (17700), 247 (13400); IR (KBr) ν_{\max} 3427, 2971, 2933, 2878, 2858, 1709, 1457, 1377, 1186, 1023 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.95 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.52 (1H, dtt, J = 10.9, 7.2, 1.4 Hz, H-12), 5.39 (1H, dtt, J = 10.9, 7.1, 1.2 Hz, H-13), 4.18 (1H, ddt, J = 3.4, 0.4, 6.7 Hz, H-15), 2.71 (3H, s, H-21), 2.51 (1H, bq, J = 6.8 Hz, H-8), 2.48 (1H, dq, J = 17.7, 7.4 Hz, H-6a), 2.41 (1H, dq, J = 17.7, 7.2 Hz, H-6b), 2.39 (2H, ddd, J = 7.1, 6.7, 1.4 Hz, H-14), 2.06 (2H, ddt, J = 7.2, 1.2, 7.0 Hz, H-11), 2.05 (3H, d, J = 1.4 Hz, H-27), 1.81 (1H, d, J = 3.4 Hz, 15-OH), 1.66 (1H, m, H-9a), 1.32 (1H, m, H-9b), 1.31 (2H, m, H-10), 1.06 (3H, d, J = 6.9 Hz, H-25), 1.04 (3H, dd, J = 7.4, 7.2 Hz, H-24); ¹³C NMR (CDCl₃, 75 MHz) δ 215.3 (s, C-7), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 132.7 (d, C-12), 125.3 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 46.0 (d, C-8), 34.3 (t, C-14), 33.5 (t, C-6), 32.7 (t, C-9), 27.5 (t, C-11), 27.3 (t, C-10), 19.2 (q, C-21), 16.5 (q, C-25), 14.4 (q, C-27), 7.8 (q, C-24); EIMS *m/z* 335 [M]⁺ (2), 317 (4), 170 (27), 169 (67), 168 (100), 140 (20); HREIMS *m/z* 335.1912 (calcd. for C₁₉H₂₉NO₂S, 335.1919).
- [0035] (39): colorless amorphous solid; $[\alpha]_D^{22}$ +26.4 (c 0.27, MeOH); UV (MeOH) λ_{\max} nm (ε) 203 (19100), 244 (12500); IR (KBr) ν_{\max} 3430, 2970, 2934, 2877, 1710, 1458, 1377, 1184 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.17 (1H, t, J = 7.3 Hz, H-13), 4.13 (1H, m, H-15), 2.70 (3H, s, H-21), 2.51 (1H, bq, J = 6.8 Hz, H-8), 2.47 (1H, dq, J = 17.7, 7.2 Hz, H-6a), 2.41 (1H, dq, J = 17.7, 7.2 Hz, H-6b), 2.33 (2H, bdd, J = 7.3, 6.8 Hz, H-14), 2.05 (3H, d, J = 1.2 Hz, H-27), 2.03 (2H, m, H-11), 1.71 (1H, d, J = 3.2 Hz, 15-OH), 1.69 (3H, d, J = 1.3 Hz, H-26), 1.62 (1H, in, H-9a), 1.32 (3H, m, H-10 and H-9b), 1.06 (3H, d, J = 6.9 Hz, H-25), 1.03 (3H, t, J = 7.2 Hz, H-24); EIMS *m/z* 349 [M]⁺ (0.7), 331 (1.7), 168 (100), 140 (5.1); HREIMS *m/z* 349.XXX (calcd. for C₂₀H₃₁NO₂S, 349.XXX).

Tab 1.

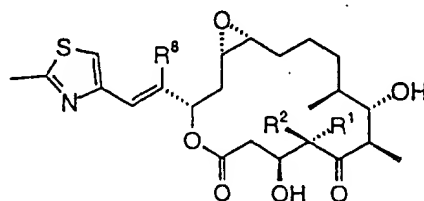
Struktur-typ	Epothilone				
	A _Y	B _Y	C _Y	D _Y	trans C _Y
Ausgangsepothilon	(1) 4	(2) 1-2	(14) 50-100	(15) 20	-
21-Hydroxy (E&F)	(3) 10	(4) 1.5	-	-	-
Oxazoles (G&H)	(10) 6	(11) 1	(12) 120	(13) 11	-

Tab 1. (fortgesetzt)

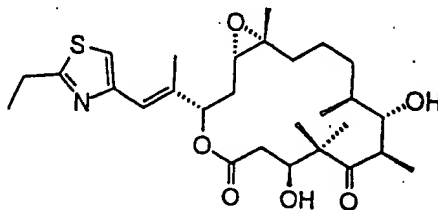
Aktivität von Epothilonen und Verbindungen (1) bis (39) gegen Maus-Fibroblasten (L929, IC50 /ng/ml/)					
Struktur-typ	Epothilone				
	A _Y	B _Y	C _Y	D _Y	trans C _Y
Ausgangsepothilon	(1) 4	(2) 1-2	(14) 50-100	(15) 20	-
(R)-4-Desmethyl (X ₁)	(5) 20	-	(16) 200	(17) 20	(28) 400
(S)-4-Desmethyl (X ₂)	(6) 7	-	(18) 25-30	(19) 12	(29) 80
6-Desmethyl (X ₃)	-	-	(20) 1500	-	-
8-Desmethyl (X ₄)	-	-	(21) 800	-	-
8,9-Dehydro (X ₅)	-	-	(22) 1500	(23) 200	-
10,11-Dehydro (X ₆)	-	-	(24) 120	-	-
14-Hydroxy (X ₇)	-	-	(25)	-	-
16-Desmethyl (X ₈)	(7) 20	-	(26) 250	-	-
27-Hydroxy (X ₉)	(8) 100	-	(27) 200	-	-
21-Methyl (X ₁₀)	-	(9) 1.5	-	-	-
Verbindung	-	-	(36) 180	-	-
Verbindung	-	-	(37) 50	-	-
Verbindung	-	-	(38) 2000	(39) 500	-

Patentansprüche

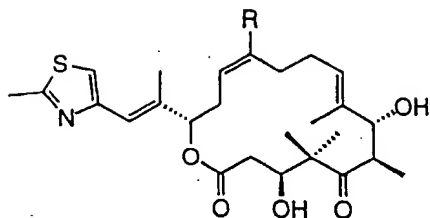
1. Epothilon der Formel

Epothilone A₉ (8) R¹ = CH₂OH; R², R⁸ = Me

2. Epothilon der Formel

Epothilone B₁₀ (9)

3. Epothilon der Formel

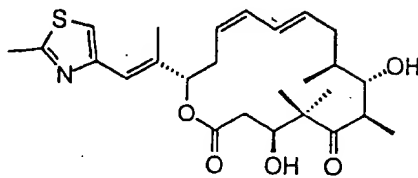


Epothilone C₅ (22) R = H

Epothilone D₅ (23) R = Me

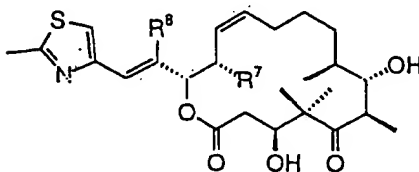
oder

4. Epothilon der Formel



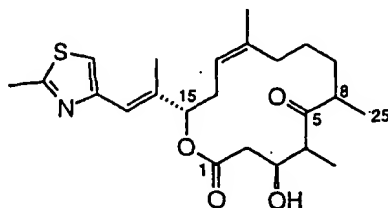
Epothilone C₆ (24)

5. Epothilon der Formel



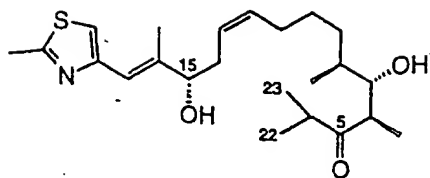
Epothilone C₉ (27) R⁸ = CH₂OH; R⁷ = H

6. Epothilon der Formel



Epothilone K (36)

7. Verbindung der Formel



(37)

Fig. 1

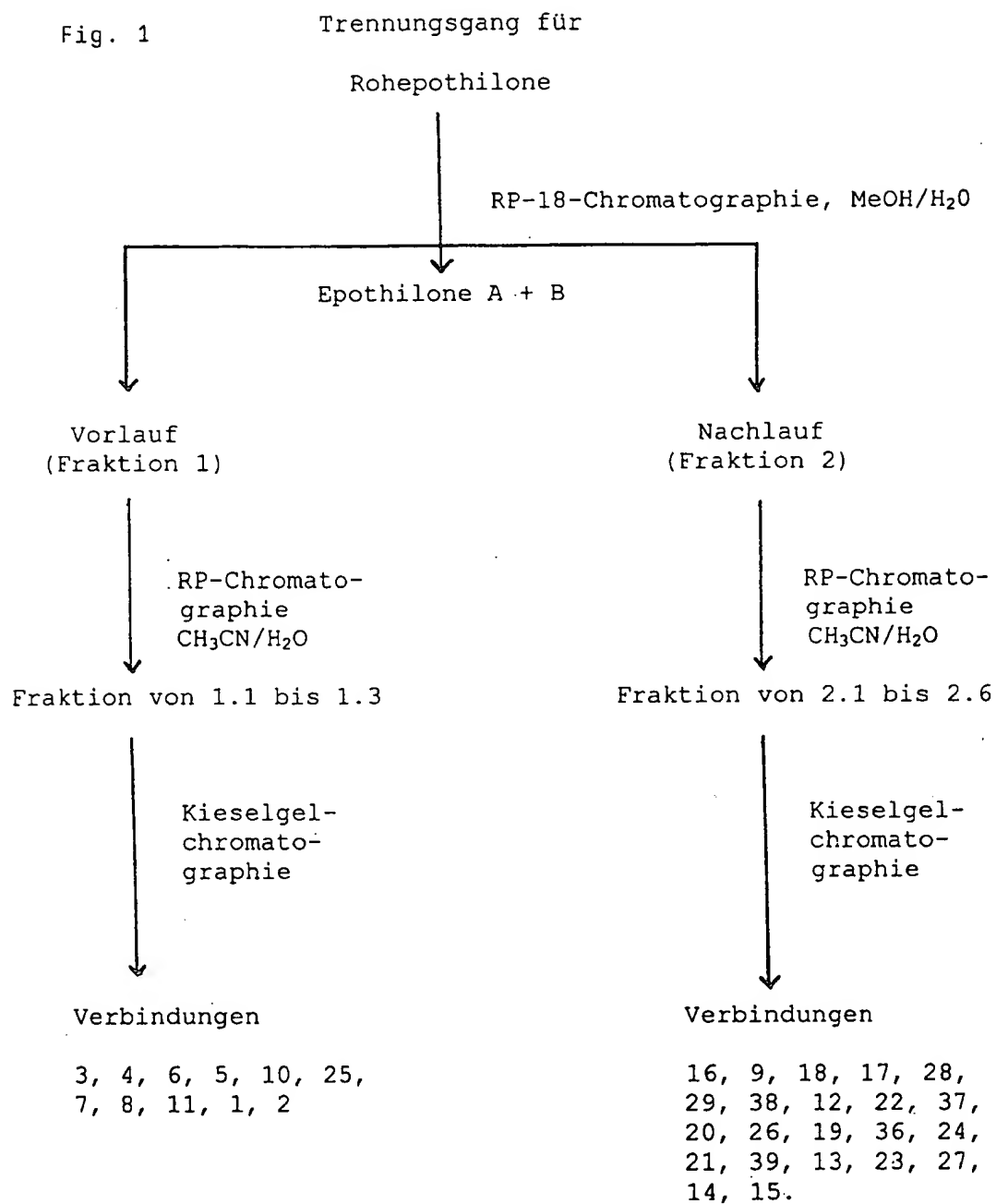


Fig. 2

fraction 1	1.1	Epothilone E (3)	variable ^a
		Epothilone F (4)	variable ^a
		Epothilone A ₂ (6)	14.5 mg
		Epothilone A ₁ (5)	3.1 mg
		Epothilone G ₁ (10)	52.3 mg
	1.2	Epothilone C ₇ (25)	0.8 mg
		Epothilone A ₂ (7)	38.7 mg
	1.3	Epothilone A ₂ (8)	4.4 mg
		Epothilone G ₂ (11)	9.4 mg
		Epothilone A (1)	29800.0 mg
fraction 2	2.1	Epothilone B (2)	10300.0 mg
		Epothilone C ₁ (16)	32.4 mg
	2.2	Epothilone B ₁₀ (9)	1.1 mg
		Epothilone C ₂ (18)	58.4 mg
	2.3	Epothilone D ₁ (17)	5.3 mg
		trans-Epothilone C ₁ (28)	1.4 mg
		trans-Epothilone C ₂ (29)	4.5 mg
		38	6.6 mg
		Epothilone H ₁ (12)	3.0 mg
		Epothilone C ₆ (22)	7.3 mg
	2.4	37	2.9 mg
		Epothilone C ₃ (20)	32.5 mg
		Epothilone C ₈ (26)	26.3 mg
	2.5	Epothilone D ₂ (19)	13.1 mg
		Epothilone K (36)	0.4 mg
		Epothilone C ₈ (24)	2.9 mg
		Epothilone C ₄ (21)	6.5 mg
	2.6	39	0.8 mg
		Epothilone H ₂ (13)	1.5 mg
		Epothilone D ₃ (23)	0.9 mg
		Epothilone C ₉ (27)	3.0 mg
		Epothilone C (14)	4600.0 mg
		Epothilone D (15)	2700.0 mg



Europäisches
Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 02 02 2332

EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int.Cl.7)
A	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5. März 1998 (1998-03-05) * Zusammenfassung; Ansprüche; Beispiele *	1-7	C07D493/04 C07D417/06 C07D413/06 C07D277/24 //(C07D493/04, 313:00,303:00)
A	WO 98 22461 A (BIOTECHNOLOG FORSCHUNG GMBH ;GERTH KLAUS (DE); HOEFLE GERHARD (DE)) 28. Mai 1998 (1998-05-28) * Zusammenfassung; Ansprüche; Beispiele *	1-7	
A	WO 97 19086 A (BIOTECHNOLOG FORSCHUNG GMBH ;KIFFE MICHAEL (DE); HOEFLE GERHARD (D)) 29. Mai 1997 (1997-05-29) * Zusammenfassung; Ansprüche; Beispiele *	1-7	
Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt			RECHERCHIERTE SACHGEBIETE (Int.Cl.7)
			C07D
Recherchenort DEN HAAG		Abschlußdatum der Recherche 21. November 2002	
		Prüfer Chouly, J	
KATEGORIE DER GENANNTEN DOKUMENTE X : von besonderer Bedeutung allein betrachtet Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie A : technologischer Hintergrund O : mündliche Offenbarung P : Zwischenliteratur T : der Erfindung zugrunde liegende Theorien oder Grundsätze E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist D : in der Anmeldung angeführtes Dokument L : aus anderen Gründen angeführtes Dokument & : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument			

EPO FORM 1503 03 02 (P04C03)

**ANHANG ZUM EUROPÄISCHEN RECHERCHENBERICHT
 ÜBER DIE EUROPÄISCHE PATENTANMELDUNG NR.**

EP 02 02 2332

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten europäischen Recherchenbericht angeführten Patentedokumente angegeben.
 Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am
 Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

21-11-2002

Im Recherchenbericht angeführtes Patentedokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
WO 9808849 A	05-03-1998	DE 19636343 C1	23-10-1997
		DE 19645361 A1	30-04-1998
		DE 19645362 A1	30-04-1998
		AU 716610 B2	02-03-2000
		AU 2149397 A	19-03-1998
		WO 9808849 A1	05-03-1998
		EP 0923583 A1	23-06-1999
		JP 2001500851 T	23-01-2001
		NZ 334821 A	22-12-2000
		US 6043372 A	28-03-2000
		US 6156905 A	05-12-2000
		US 5969145 A	19-10-1999
WO 9822461 A	28-05-1998	AU 753546 B2	24-10-2002
		AU 5483798 A	10-06-1998
		BR 9713363 A	25-01-2000
		CN 1237970 A	08-12-1999
		CZ 9901750 A3	15-09-1999
		WO 9822461 A1	28-05-1998
		EP 0941227 A1	15-09-1999
		HU 0000497 A2	28-06-2000
		IL 129558 A	31-10-2001
		JP 2001504474 T	03-04-2001
		NO 992338 A	14-05-1999
		NZ 335383 A	27-10-2000
		PL 333435 A1	06-12-1999
		TW 408119 B	11-10-2000
		ZA 9710384 A	18-05-1999
WO 9719086 A	29-05-1997	DE 19542986 A1	22-05-1997
		DE 19639456 A1	26-03-1998
		AT 218556 T	15-06-2002
		DE 59609305 D1	11-07-2002
		DK 903348 T3	16-09-2002
		WO 9719086 A1	29-05-1997
		EP 1186606 A1	13-03-2002
		EP 0873341 A1	28-10-1998
		EP 0903348 A1	24-03-1999
		JP 2000500757 T	25-01-2000
		US 6288237 B1	11-09-2001
		US 2001034452 A1	25-10-2001

EPO FORM P0461

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr. 12/82